REMARKS

Claims 63-65, 67, 70-78, and 84-92 are pending. Claims 63-65, 67, 70, 71, 74, 77, 78, 84-88, and 90 are rejected under 35 U.S.C. § 112, first paragraph. Claims 72, 73, 75, 76, 88, and 89 are objected to. Applicants address each basis for rejection as follows.

Claim status

Applicants note that claim 88 is included in the claims rejected under 35 U.S.C. § 112, first paragraph, but is also listed as being objected to for depending from a rejected claim. As claim 88 recites the same amino acid sequence of claim 72, Applicants submit that claim 88, like claim 72, is not subject to the present rejection under 35 U.S.C. § 112, first paragraph.

Applicants also note that the Office Action does not list claims 91 and 92 as being rejected or objected to. Claims 91 and 92 recite the same amino acid sequences as claims 75 and 76, respectively, and therefore Applicants submit that claims 91 and 92, like claims 75 and 76, are also not subject to the present rejection under 35 U.S.C. § 112, first paragraph and should be listed as objected to for depending from a rejected claim.

Claim amendments

Claims 63 and 85 have been amended to recite that the proteinaceous recognition domain consists of a peptide of five to sixty amino acids, and claims 64 has been

amended to recite that the proteinaceous recognition domain consists of a peptide of ten to forty amino acids. No new matter has been added by the present amendment.

Applicants reserve the right to pursue any cancelled subject matter in this or in a continuing application.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 63-65, 67, 70, 71, 74, 77, 78, 84-88, and 90 are rejected under 35 U.S.C. § 112, first paragraph, for an asserted lack of written description and enablement in the specification as filed. Applicants address these bases for rejection, in turn, below.

Written description

The Office states (page 3):

> The claimed invention encompasses a large variable genus of proteins. The claims encompass a peptide aptamer (intracellular recognition molecule) and any target bound to any TRX-like protein as a platform interacting with an unspecified amount of targets (see claim 63 for example); and the claims encompass any intracellular recognition molecules and any target bound to any platform having the capacity to interact with the unspecified amount of targets. The claims are also drawn to any peptide having 5 to 60 amino acids. Note that the word "having" is open thus said peptide is limitless.

The standard for adequate written description is whether the description clearly allows persons of ordinary skill in the art to recognize that one has invented what is claimed (see, e.g., M.P.E.P. (Eighth Edition, Rev. 5, August 2006) § 2163.02). In applying this standard, the Federal Circuit has held:

> If a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met. *In re Alton*, 76 F.3d 1168, 1177, 37 U.S.P.Q.2d 1578 (Fed. Cir. 1996).

And, the Guidelines, under the "Genus Analysis" decision tree, state:

> What is a representative number of species depends on whether one of skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed or claimed.

Applicants' specification, for the reasons detailed below, meets these standards for the claimed invention.

Applicants note that the claims as amended are directed to an intracellular recognition molecule R, including a proteinaceous recognition domain, conformationally constrained by covalent bonding to a platform. The recognition molecule R specifically interacts within a cell with a site on a predetermined intracellular target molecule T, and the interaction with T occurs with an affinity corresponding to a K_d value between 1×10^{-9} M and 1×10^{-14} M (claim 63) or between 5×10^{-9} M and 1×10^{-14} M (claim 85), where (1) *the intracellular recognition molecule R is a peptide aptamer*, where (2) the platform is thioredoxin or a thioredoxin-like protein (claim 63) or thioredoxin, a human thioredoxin, or a glutaredoxin (claim 85), and where (3) the proteinaceous recognition domain consists of a peptide of five to sixty amino acids.

Applicants note that the claims are not directed to "any intracellular recognition molecules," but rather to intracellular recognition molecules that are peptide aptamers.

Also, the claims as amended require the peptide aptamers to be between five and sixty (claims 63 and 85) or between ten and forty (claim 64) amino acids in length. As stated, for example, at the top of page 3 of the specification, the present invention stems from the finding that, for any given target molecule, a peptide aptamer recognition molecule that interacts with the target with a K_d of less than 1×10^{-9} may be designed. The specification as filed describes various peptide aptamers that are encompassed by the claims. For instance, in Example 1, the specification describes anti-Cdk2 aptamers and in Example 4, the specification describes anti-Bax aptamers. Moreover, for example, at the bottom of page 59, to the top of page 62, the specification describes methods that can be used to generate and modify aptamers. One skilled in the art would recognize that these techniques are applicable to any number of proteins. As such, Applicants submit that the description in the specification of aptamers is not limited to the particular recited examples, but rather provides adequate description of peptide aptamers in general.

With regard to the platform, Applicants note that claim 63 requires the platform to be thioredoxin or a thioredoxin-like protein. The structure of thioredoxin from various species was known at the time of filing (as described, for example, at the top of page 15 of the specification). In addition, the structure of thioredoxin-like proteins having a three-dimensional structure substantially similar to that of thioredoxin (e.g., glutaredoxin) was also known at the time of filing (see, e.g., the top of page 15). As such, the specification describes that thioredoxin and thioredoxin-like proteins can be used to conformationally

constrain the intracellular recognition molecule. One skilled in the art would recognize that the exact sequence of the platform is not critical so long as it can function to conformationally constrain the intracellular recognition molecule. In fact, the specification, at page 14, in the second full paragraph, states that the platform "can be any molecule which is capable of reducing, through covalent bonding, the number of conformations which [the intracellular recognition molecule] can assume" and provides numerous examples of conformation constraining proteins and peptides including thioredoxin and thioredoxin-like proteins. Further, in the March 3, 2006 reply, Applicants submitted evidence in support of the term "thioredoxin-like protein" being well known in this art, and those skilled in the art therefore recognizing what "thioredoxin-like proteins" are. Given the knowledge in the art of thioredoxin, thioredoxin-like proteins, and their structure, Applicants submit that one skilled in the art would recognize that Applicants were in possession of the genus of thioredoxin-like proteins. The claims should not be limited to particular thioredoxin-like proteins.

Turning to claim 85, Applicants note that claim 85 requires the platform to be thioredoxin, a human thioredoxin, or a glutaredoxin. As noted above, the specification teaches that the sequence and structure of thioredoxin and glutaredoxin were known in the art at the time of filing. There can be no question that the platform proteins recited in claim 85 are described in the application as filed. This basis of the written description rejection of claim 85 and its dependent claims should be withdrawn.

Applicants submit that the target is also adequately described in the specification as filed. In the first full paragraph at page 26, the specification states that the target molecule "can be any intracellular molecule." The claims require the intracellular recognition molecule to interact with the target. As such, the target is defined by reference to the intracellular recognition molecule. The intracellular recognition molecule, as noted above, is a peptide aptamer, and the target is limited to intracellular molecules that interact with the peptide aptamer with a particular affinity (e.g., between 1 x 10^{-9} and 1 x 10^{-14} in claim 63). The specification, for instance, in Examples 1-5, teaches how to generate peptide aptamers and how to modify such aptamers to increase their affinity for a given target molecule. In particular, the specification, for example, in Table 1 at pages 44 and 45, describes a modified anti-Cdk2 aptamer that binds its target with a Kd of between 1 x 10^{-9} and 1 x 10^{-14}. In view of the teachings in the specification as to how aptamers may be made and modified to bind to any target and Applicants' teachings that the target may be any intracellular molecule, Applicants submit that one skilled in the art would recognize that the target described in the specification as filed, and encompassed by the claims, is not limited to a particular intracellular molecule.

For all of the above reasons, Applicants submit that the specification satisfies the written description requirement set forth by the case law and the written description guidelines. This basis for the 35 U.S.C. § 112, first paragraph, rejection may be withdrawn.

Enablement

The Office states (page 5):

> [T]he specification, while being enabling for intracellular recognition molecules that are peptide aptamers ... does not reasonably provide enablement for any intracellular recognition molecule or target or TRX-like protein.

As an initial matter, as indicated above, Applicants note that the independent claims (claims 63 and 85) require the intracellular recognition molecule to be a peptide aptamer. As such, Applicants submit that the intracellular recognition molecules encompassed by the claims are ones which the Office has indicated to be enabled by Applicants' specification. Nonetheless, the Office with respect to the recognition domain at page 7, also asserts that the claims recite "open and closed language in association with the structure and there is no indicia as to whether the structure once modified will function or have biological activity."

The claims as amended require the proteinaceous recognition domain to consist of a peptide of five to sixty amino acids (claims 63 and 85) or of a peptide of ten to forty amino acids (claim 64). Hence, the claims provide a defined length for the recognition domain. Moreover, the specification in Examples 1-5 describes methods that may be used to modify a recognition domain and to test its activity, and also describes examples of aptamers that have been modified and, after testing, have been found to bind their target with higher affinity (see, e.g., the anti-Cdk2 aptamers described in Example 1 and the anti-Bax aptamers described in Example 4). As such, the specification describes how

one skilled in the art can make and use the peptide aptamers recited in the claims.

On this point, Applicants also direct the Office's attention to the Declaration of Dr. Pierre Colas filed on May 6, 2005 in which Dr. Colas states that, besides the anti-Cdk2 and anti-Bax aptamers described in the Examples, he successfully selected peptide aptamers against the GTPase activating protein RasGAP, the transcriptional repressor Fur, the adaptor protein Grb2, the protein kinases Raf, ERK1, and AKT1, and the chaperone Hsp70 using the two-hybrid system disclosed in the present application. Clearly the specification as filed enables the generation of peptide aptamer recognition molecules against a wide variety of proteins.

Furthermore, Applicants note that M.P.E.P. (Eighth Edition, Rev. 5, August 2006) § 2164.08(b) states: "The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled." As was stated in *In re Wands,* 858 F.2d. 713, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988), "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." Moreover, it is improper to find that such experimentation is "undue" simply because it requires some "trial and error." *W.L. Gore & Assoc. v. Garlock, Inc.* 721 F.2d 1540, 1557, 220 U.S.P.Q. 303, 316 (Fed. Cir. 1983). This is true even when the experimentation is needed to weed out inoperative embodiments. *Atlas Powder v. E.I. DuPont deNemours*, 750 F.2d 1569, 1576-77, 224

U.S.P.Q. 409, 414 (Fed. Cir. 1984).

Given that the claims recite particular lengths for the peptide aptamer recognition molecule and provide extensive teachings and examples as to how such recognition molecules may be modified and tested, Applicants submit that making and using the recognition molecules encompassed by the claims does not require undue experimentation. This basis of the enablement rejection may be withdrawn.

The thioredoxin-like molecules recited in the claims are also enabled by the specification as filed. The specification states (page 15):

> Thioredoxin-like proteins are defined herein as proteins having at least 18%, preferably at least 40% and more preferably at least 75% homology with the amino acid sequence of *E. coli* thioredoxin over an amino acid sequence length of 80 amino acids. Thioredoxin-like molecules also include peptides which have a three-dimensional structure substantially similar to that of human or *E. coli* thioredoxin, for example glutaredoxin. (Citations omitted.)

Moreover, as noted above, in the March 3, 2006 reply, Applicants submitted evidence showing that the term "thioredoxin-like protein" is well known in this art, and therefore those skilled in the art would know what "thioredoxin-like proteins" are and could make and use them accordingly.

The Office asserts that due to the variability of thioredoxin-like molecules encompassed by the claims, "the desired effect of bonding of the recognition molecule R to the platform may not occur." Applicants again note that the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled

and that a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

As noted above, the sequence and structure of thioredoxin was known at the time the application was filed. Similarly, the sequence and structure of glutaredoxin (a thioredoxin-like molecule) was known at the time of filing. Given these known sequences and structures and the teachings in Applicants' specification, Applicants submit that one skilled in the art could readily have obtained other thioredoxin-like sequences without undue experimentation using nothing more than techniques standard in the art of molecular biology. Moreover, the specification, for example, at the bottom of page 13, teaches how to conformationally constrain an aptamer in a platform (e.g., a thioredoxin-like protein) and, for example, at pages 62-63 describes how an interaction between an aptamer and its target may be assayed using a yeast two-hybrid system. As such, any inoperative thioredoxin-like molecules can readily be removed without undue experimentation.

Finally, with regard to the target, Applicants note that, as stated in the specification at page 26, any intracellular molecule may be the target. Selecting a target that binds the peptide aptamer intracellular recognition molecule with the required affinity does not require undue experimentation. The specification, for example, at page 31, describes screening a "pool of random peptides in a cell against an unknown or known endogenous

target molecule T, wherein interaction with T gives rise to a detectable or selectable phenotypic change." In addition, in the Examples, Applicants describe using yeast two-hybrid assays to characterize the interaction between peptide aptamers and their targets. Any intracellular target molecule may be used in these assays. This basis for the enablement rejection may also be withdrawn.

CONCLUSION

Applicants submit that the application is now in condition for allowance, and this action is hereby respectfully requested.

Enclosed is a Petition to extend the period for replying to the Office Action for three (3) months, to and including August 20, 2007, and a check in payment of the required extension fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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